

Melatonin for the newborn

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The last ten years, the next ten years in Neonatology

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Abstract

Reactive oxygen species play an important role in the pathogenesis of several diseases during the perinatal and neonatal period. Melatonin, an effective direct free-radical scavenger and indirect antioxidant agent, diffuses through biological membranes easily and exerts pleiotropic actions on every cell. Several studies have tested the efficacy of melatonin to counteract oxidative damage in diseases of newborn such as chronic lung disease, perinatal brain injury, necrotizing enterocolitis and sepsis, giving promising results. The peculiar perinatal susceptibility to oxidative stress indicates that prophylactic use of antioxidants as melatonin could help to prevent or at least reduce oxidative stress related diseases in newborns. However, more studies are needed to confirm these beneficial effects.

Keywords

Melatonin, asphyxia, respiratory disease, necrotizing enterocolitis, analgesia, sepsis.

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Introduction

Melatonin is an endogenously produced indolamine principally synthesized in the pineal gland from the neurotransmitter serotonin [1]. It has recently been recognised as a “ubiquitously distributed and functionally diverse molecule” [2]. In fact, melatonin plays a key role in a variety of important physiological functions, including regulation of circadian rhythms, as well as visual, reproductive, cerebrovascular, neuroendocrine and neuroimmunological actions [3]. Furthermore, melatonin is a highly effective antioxidant and free-radical scavenger [1]. Free-radicals are oxygen- and nitrogen-derived metabolites, collectively termed reactive oxygen species (ROS) and reactive nitrogen species (RNS), persistently produced in aerobic organisms. When generated in excess, ROS/RNS mutilate molecules and are important mediators of cell and tissue damage [4, 5]. The resulting damage, which is unavoidable, is referred to as oxidative stress (OS) caused by free radicals. It is by now well known that melatonin directly scavenges ROS detoxifying against the highly reactive hydroxyl radicals. Melatonin and its metabolites efficiently interact with various ROS/RNS as well as with organic radicals, upregulates antioxidant enzymes (including glutathione peroxidases and glutathione reductase), and down regulates pro-oxidant enzymes (nitric oxide synthases and lipoxygenases) [6]. Thus, melatonin prevents lipid peroxidation (LPO), reduces mitochondrial hydroperoxide levels and restores glutathione homeostasis (GSH) [7]. High endogenous melatonin levels have been observed in critically-ill children in comparison to normal age-matched subjects and this finding has been considered as a response to counteract the elevated OS associated with serious diseases [8].

Melatonin in perinatal period

During pregnancy, increased oxygen demand augments the rate of production of ROS and women, even during normal pregnancies, experience elevated OS compared with non-pregnant women [9]. Increased levels of OS and reduced antioxidative capacities may contribute to the pathogenesis of maternal and perinatal disorders, as newborns are more prone to OS than individuals later in life. ROS generation is further elevated in the placenta during preeclampsia and intrauterine fetal growth retardation (IUGR) [10, 11]. Reduced levels of melatonin have been found in pregnant

women with preeclampsia, suggesting a role in the pathogenesis of this disease. Also, pregnant women with lower melatonin levels had a higher risk of developing preeclampsia [12]. Therefore, in preeclampsia a deficiency of melatonin would explain the suppressed antioxidant capacity [13, 14]. Furthermore, melatonin plays an important role in controlling blood pressure [15]. The use of melatonin as an antenatal antioxidant therapy in IUGR has been proposed as a promising and safe option to protect the fetal brain from injury. Miller et al. [16] evaluated the effects of oral melatonin administration to women with an IUGR fetus and showed that maternal melatonin, well tolerated by both mother and fetus, increased fetal melatonin levels and reduced OS in the placenta, as evidenced by reduced MDA levels, compared to IUGR pregnancies untreated with antenatal melatonin. IUGR in human infants has been associated with a reduction in melatonin secretion during the first 3 months of life [17]. Furthermore, 6-sulphatoxylmelatonin (6SaMT), a urinary melatonin metabolite, is impaired in adults who were growth restricted prenatally or were born after 40 weeks of gestation [17].

Melatonin synthesis has been identified in the placenta and the villous trophoblasts contain the classic transmembrane receptors for the indole, MT1 and MT2 [18].

Melatonin, in addition to its local production, readily crosses the placenta and does not harm the developing fetus, not even when administered in extremely high doses [19]. Fetal melatonin is of maternal origin and it undergoes circadian fluctuations in synchrony with the day-night rhythm [20]. Melatonin levels increase gradually from 24 weeks of gestation and reach highest levels during the third trimester, returning to baseline levels by the second day of puerperium [21]. In the last trimester of pregnancy, the fetus develops a biological clock that is responsive to maternal circadian rhythms with fluctuations in hormonal levels, behaviour, and sleep [22]. After birth, the full-term neonate does not produce melatonin for 3-5 months, leading to transient melatonin deficiency [23]. Melatonin rhythmicity is established at about 8 to 12 weeks after a term delivery [23]. Prematurity itself does not hasten the maturation of the neurological network controlling melatonin secretion, rather the onset of pineal melatonin secretion is even more delayed when there is exposure to neurological insults. Thus, in premature neonates, the melatonin deficiency is more prolonged [24].

The use of melatonin treatment during the late fetal and early neonatal period might result in a wide range of health benefits, improve quality of life and may help limit complications during the critical periods prior to and shortly after delivery. In light of its properties melatonin has been used as an adjuvant in the treatment of free radical disease in the newborn, and several evidences suggest a role for melatonin in perinatal disorders, including asphyxia, respiratory distress syndrome (RDS), surgical processes, and sepsis [25-29]. Moreover, since preterm infants are melatonin deficient, administration of the compound may provide the necessary levels to assure their health and well-being [30].

Asphyxia

Injury to the fetal brain is a major contributor to morbidity and mortality in preterm and term [31] infants. Neonatal hemorrhagic brain injury (such as intraventricular hemorrhage) [32] and white matter brain injury (such as periventricular leukomalacia) are often cause of long term neurosensory disabilities, including cerebral palsy. The pathogenesis of brain injury is known to be complex and multifactorial, with a number of interrelated pathways contributing to central nervous system cellular dysfunction and, in this contest, the free radical induced damage appears to have a crucial role [33]. Neuropathological studies indicate that many critical neuronal groups are more vulnerable to hypoxic-ischemic injury in newborns (immature brain) than in adults, particularly related to enhanced density and function of excitatory amino acid receptors as well as enhanced vulnerability to attack by ROS and RNS [34]. During the last decade, melatonin has started to be considered as an attractive option in order to minimize as much as possible the neurological sequelae from hypoxic-ischemic brain injury, because of its ability to cross all physiological barriers reaching subcellular compartments, its efficacy and safety profile [35-38].

The neuroprotective effects of melatonin in the fetal brain have been assessed in many animal models. Following intrauterine asphyxia (*via* umbilical cord occlusion), melatonin administration to both preterm and near-term fetal sheep has been shown to reduce OS [39] and attenuate cell death (including apoptosis) in the fetal brain, in association with a reduced inflammatory response [40]. Systemic administration of melatonin

following acute neonatal hemorrhagic brain injury in rats has additionally been shown to protect against post-hemorrhagic consequences of brain atrophy [32]. Importantly, melatonin has been shown to improve functional outcomes following such brain injury – ameliorating cognitive and sensorimotor dysfunction in the juvenile rat [32]. Fulia et al. [41], in the first study where melatonin was given to human newborns, demonstrated the reduction of MDA and nitrite/nitrate levels in the serum of asphyxiated newborns after treatment with melatonin given within the first 6 hours of life [41]. Currently, hypothermia is recognized as an efficacious treatment modality for neonatal hypoxic-ischemic encephalopathy. The use of synergic strategies, such as the association between hypothermia and melatonin supplementation, may lead to a larger neuroprotective effect on the brain, thus improving the neonatal outcome. In this regard, Robertson et al. [42] have recently shown that melatonin administration to newborn piglets augments hypothermic neuroprotection by improving cerebral energy metabolism and by reducing brain damage.

Respiratory disease

Elevated OS and/or reduced endogenous antioxidant defenses may also play a role in the pathogenesis of a number of inflammatory pulmonary diseases, including RDS in the newborn [43]. Although oxygen therapy is essential in the treatment of respiratory disorders of newborn, hyperoxic exposure itself induces excessive production of ROS/RNS in the respiratory system. The exposure of immature lungs to prolonged periods of high levels of inspired oxygen is accepted as an important contributor to the development of chronic lung disease (CLD).

Melatonin has been used for RDS of newborns and bronchopulmonary dysplasia. Gitto et al. [26] examined whether melatonin treatment would lower proinflammatory cytokines, interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor α (TNF- α), and nitrite/nitrate levels in 24 newborns with RDS grade III or IV diagnosed within the first 6 hours of life; they concluded that melatonin treatment reduced the proinflammatory cytokines and improved the clinical outcome.

It is well known that pulmonary damage depends in large part on the ventilatory strategies used. In particular, it was demonstrated that newborns mechanically ventilated in pressure support

ventilation mode with guarantee volume and receiving melatonin presented a greater reduction of serum levels of inflammatory cytokines than did newborns ventilated in conventional mode or in oscillatory ventilation receiving melatonin or diluent alone [44]. Thus the antioxidant and anti-inflammatory effects of melatonin could be effective in the prevention of CLD in ventilated newborns.

Necrotizing enterocolitis

Melatonin is also produced in a variety of tissues including the intestines, especially after feeding, mainly in serotonin-rich enteroendocrine cells (enterochromaffin cells) [45]. The beneficial effects of melatonin in preventing gastrointestinal disturbances were studied in mice [46, 47].

Necrotizing enterocolitis (NEC) is primarily a disease process of the gastrointestinal tract of premature neonates that results in inflammation and bacterial invasion of the bowel wall. Perrone et al. showed that the determination of oxidative-stress biomarkers can be useful in identifying babies at high risk for NEC [48]. Studies demonstrate that TNF- α and interleukin 1 β (IL-1 β) were reduced in animal model affected NEC and treated with melatonin [46]. The major mechanism of melatonin on cytoprotection effect includes free radical scavenging activity and activation of cyclooxygenase-prostaglandin enzyme system, exerting cytoprotective and inflammation activities on gastrointestinal system mucosa. On NEC model in newborn rats it has been used the combination of melatonin and prostaglandin [45]. Based on these observations, melatonin should be considered as a potentially safe approach to NEC treatment in infants.

Sepsis

Clinical studies are consistent with the involvement of ROS/RNS in neonatal sepsis and its complications. Melatonin accumulates in mitochondria [49], and both it and its metabolites have potent antioxidant and anti-inflammatory activities and may be useful in sepsis [50]. *In vitro* models of sepsis show that melatonin and its major hydroxylated metabolite, 6-hydroxymelatonin, are both effective at reducing the levels of inflammatory cytokines and mitochondrial dysfunction [51, 52]. In rat models of sepsis, melatonin reduces oxidative damage and organ dysfunction and also decreases mortality [53, 54]. Batra et al. [55] documented increased production of oxygen derived reactants in

septic neonates. Furthermore, the role of melatonin in the reduction of OS in septic neonates has been shown. Gitto et al. [29] assessed the efficacy of antioxidant therapy with melatonin in neonates with sepsis. Serum levels of LPO products (MDA and 4-hydroxylalkanal [4-HDA]) were examined before and after 1 and 4 h of melatonin treatment. Clinical status and sepsis related serum parameters were also evaluated at 24 and 48 h after melatonin administration. They founded that serum MDA and 4-HDA concentrations in septic newborns were significantly higher than those in healthy infants; in contrast, in newborns treated with melatonin there was a significant reduction of MDA and 4-HDA to the levels in the normal controls. Melatonin also improved the clinical outcome of the septic newborns as judged by measurement of sepsis-related serum parameters after 24 and 48 h. This study demonstrated that this indoleamine is effective in neonates with septicemia by reducing the levels of LPO products, thereby improving clinical status of neonates [29].

Analgesia

Newborns and infants who require intensive care are often exposed to painful procedures. The immediate effects of painful stimuli in newborns are well known (decreased oxygenation, hemodynamic instability, and increased intracranial pressure) [56], but growing evidence shows that early pain experiences in newborn infants may have long-term consequence that alter brain development [57]. Hence, newborn pain prevention and effective treatment in Neonatal Intensive Care Units (NICUs) is recommended throughout the world. Melatonin has been shown to exert antinociceptive actions in a variety of experimental animal models and in humans, suggesting that melatonin may have promising roles as an antinociceptive therapy [58-60].

Gitto and co-workers [61] hypothesized that melatonin may have beneficial effects as an analgesic antioxidant in preterm newborns that are subject to painful procedures such as endotracheal intubation and mechanical ventilation. They evaluated the analgesic activity of melatonin using the Neonatal Infant Pain Scale (NIPS) before, during, and after 5 min of elective endotracheal intubation, and the Premature Infant Pain Profile (PIPP) score at 12, 24, 48, and 72 h during ventilation in two groups of premature neonates. In the former group 10 mg/kg of melatonin were intravenous administrated prior to intubation in addition to the standard procedural

analgesedation treatment (fentanyl); the latter group only received standard analgesedative therapy.

The levels of the pro- and anti-inflammatory cytokines (IL-6, IL-8, IL-10, and IL-12) implicated in pain response were evaluated in both groups. The pain score was similar in both groups at an early phase (NIPS), while it was lower in melatonin-treated infants at a late phase (PIPP score). Pro-inflammatory and anti-inflammatory cytokines were higher in the common sedation and analgesia group than in melatonin-treated infants. The lower level of pro-inflammatory and anti-inflammatory cytokines in these neonates suggests the use of melatonin as an adjunct analgesic therapy during procedural pain, especially when an inflammatory component is involved [61].

Conclusion

The peculiar perinatal susceptibility to OS indicates that prophylactic use of antioxidants as melatonin could help to prevent or at least reduce OS related diseases in newborns. Several studies have tested the efficacy of melatonin to counteract oxidative damage in “oxygen radical diseases of newborn” such as CLD, perinatal brain injury, NEC and sepsis, giving promising results [62]. Melatonin could be considered as a valid alternative in neonatal analgesia. However, more studies are needed to confirm the beneficial effects of melatonin in perinatal and neonatal period.

Declaration of interest

The Authors declare that there is no conflict of interests regarding the publication of this paper.

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